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PHARMACEUTICAL AND BIOLOGICAL AVAILABILITY OF SUSTAINED RELEASE PREPARATIONS OF POTASSIUM CHLORIDE

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SUMMARY

The pharmaceutical availability of two sustained release preparations of potassium chloride – one capsule containing pellets of KCl and one coated tablet – was estimated by measuring dissolution rates with the Paddle Method USP XX and the Rotation Method NF XIV. Results were compared with bioavailability studies in which the urinary excretion of potassium was measured with an atomic absorption spectrophotometer before and after oral administration of the two preparations in a randomized cross-over experiment with 10 healthy volunteers. The subjects were fed a special diet to control potassium intake and to standardize basal potassium excretion. Urinary potassium was measured for 3 days before and for 24 h after administration of the equivalent of 40 mmol K^+. Markedly different rates of release of active ingredient from the two preparations were obtained using the Rotation Method, the coated tablet showing complete release of active ingredient within 3.5 h, whilst the pellet preparation showed a sustained release over the entire 7 h period. However, both preparations showed very similar, sustained release with the Paddle Method. The similarity of the two preparations was confirmed by the bioavailability studies, in which both caused a prolonged increase in urinary potassium excretion.

INTRODUCTION

In the last few years, potassium chloride has become increasingly used to treat potassium deficiency. Unfortunately potassium supplementation is not without problems, since solutions of potassium have an unpleasant taste. Solid dosage forms, unless specially modified to give a slow release of active ingredient, can cause considerable irritation of the gastrointestinal mucosae and can even lead to necrosis and subsequent scarring (Boley et al., 1965; Wynn et al., 1965).

Such side-effects have led to the development of depot, or sustained release preparations, which slow the release of active ingredient in various ways, e.g. by embedding it in hydrophilic and lipophilic depot components. Such formulation techniques delay the rate of absorption and produce a slow release of potassium chloride during passage through

the gastrointestinal tract (Rider et al., 1975; Ben-Ishay and Engelman, 1973). In one of the depot preparations used in these investigations, Kalitrans retard, formulation was based on the concept of distributing many minute KCl-containing pellets over a large surface area in the gastrointestinal tract with then slowly release their KCl over a period of several hours. The pellets are administered in hard gelatin capsules and after their rapid disintegration, the KCl pellets are homogeneously distributed, thus avoiding high local concentrations of potassium chloride in the mucosal membrane. In comparative studies with rabbits, treatment with KCl pellets has been reported to cause less irritation of the gastric mucosa than enteric-coated and depot tablets (Beckett and Samaan, 1978).

In the present study, the pharmaceutical and biological availabilities of the pellet preparation, Kalitrans retard, have been compared with those of the depot-coated tablet, KCl retard. Pharmaceutical availability has been assessed in vitro using the Rotation Method NF XIV and the Paddle Method USP XX. Bioavailability was estimated by measuring the urinary excretion of potassium under standardized experimental conditions.

MATERIALS AND METHODS

Bioavailability investigations

Design of study

Ten healthy male and female volunteers (Table 1) were given in a randomized cross-over experiment, 40 mmol K^+ in the form of 5 × 600 mg tablets or capsules of KCl retard Zyma * or Kalitrans retard **.

The amount of potassium excreted in the urine of each subject before and after oral administration of the preparations was estimated over a 4-day period by collecting urine samples as follows:

Day 1	24 h urine
Day 2	24 h urine
Days 3 and 4	Urine fractions after 1, 2, 3, 4, 5, 6, 7, 8, 10, 12 and 24 h.

To standardize basal potassium excretion, all volunteers were fed a special diet (Table 2) so that strict control could be kept over daily potassium intake. Subjects were not allowed to take any other food or drink, but smoking was permitted.

A constant daily intake of approximately 90 mmol K^+ was maintained throughout the entire study, the first 3 days of which were used to standardize potassium intake and basal excretion. On the first two days, 24 h urine samples were collected and on the third day, samples were collected at the intervals shown above. On the fourth day, subjects received 40 mmol K^+ at 07.00 h on a fasting stomach. Urine fractions were then collected at the same intervals as on 3rd day. At least 3 days elapsed between the two test preparations.

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* KCL retard Zyma, Zyma GmbH, Munich, G.F.R.

** Kalitrans retard, Fresenius KG, Oberursel, G.F.R. based on KCl in Permecaps-controlled release form by Pharmatec, Milan, Italy.

TABLE 1

DETAILS OF SUBJECTS

Initials	Sex	Age	Weight (kg)	Height (cm)
S.L. A.	male	42	64	169
U. K.	male	31	73	175
M. L.	female	29	57	170
K. M.	female	34	55	166
G. R.	female	22	54	160
K. R.	female	26	55	165
R. Sch.	male	31	90	174
E. Schm.	female	27	52	168
U. Schm.	female	29	70	170
G. St.	male	27	78	186

Quantitative estimation of potassium in urine

Urinary potassium was estimated, after appropriate aqueous dilution, by atomic absorption spectrophotometry, using a Perkin-Elmer Atomic Absorption Spectrophotometer model 300S and a potassium-hollow cathode lamp with an air–acetylene flame. Absorption was measured at 766.5 and 404.7 nm. Results were calculated using the standard-addition method under addition of at least two concentrations of potassium. Urine samples were diluted so that the solution never contained more than 2 μg potassium/ml. Potassium is partly ionized in the air–acetylene flame. Such a reaction is usually

TABLE 2

DIET GIVEN TO SUBJECTS TO STANDARDIZE POTASSIUM INTAKE

Time	Diet
07.00	100 ml 'high' vit. C drink or 80 ml tomato juice
09.00	100 ml Bio Halbe drink [a] (1/2 drink)
10.00	100 ml 'high' vit. C drink or 80 ml tomato juice
11.00	100 ml Bio Halbe drink (1/2 drink)
12.00	100 ml 'high' vit. C drink or 80 ml tomato juice
13.00	100 ml Bio Halbe drink (1/2 drink)
14.00	100 ml 'high' vit. C drink or 80 ml tomato juice
15.00	100 ml Bio Halbe drink (1/2 drink), Bio Halbe soup (250 ml), 1 slice 'crispbread', 1 cup coffee
17.00	100 ml 'high' vit. C drink or 80 ml tomato juice
18.00	Bio Halbe cream (125 ml)
19.00	100 ml 'high' vit. C drink or 80 ml tomato juice
20.00	Bio Halbe soup (250 ml) and/or 1 omelette, 200 ml tapwater, 1 slice 'crispbread'
21.00	100 ml 'high' vit. C drink or 80 ml tomato juice

[a] The diet Bio Halbe was kindly supplied by Diasana Vertrieb GmbH, 7760 Radolfszell, G.F.R.

supressed by addition of a large excess of alkali salts. Since the urine samples, however, contain large amounts of sodium no further addition of alkali salts was deemed necessary. Spectral interference was considered unlikely. Measurement at the wavelength of 404.7 nm was around 500 times less sensitive than 766.5 nm, so measurement at the former wavelength required little, if any dilution of samples. Since the potassium content of the urine samples varied widely, measurements were generally made at 766.5 nm, and only those samples containing adequate amounts of potassium were also measured at 404.7 nm.

Evaluation of bioavailability

The bioavailability and bioequivalence of the two preparations, KCl retard Zyma and Kalitrans retard, were evaluated by compiling urinary excretion data comparing the rates of potassium excretion before and after oral administration of each preparation in each subject.

Pharmaceutical availability investigations

In vitro dissolution rates were measured using the Rotation Method NF XIV and the Paddle Method USP XX. The experimental conditions chosen for the Rotation Method were as those stated in the NF XIV, except that the potassium phosphate in the proposed dissolution medium (Intestinal Fluid USP XX) was replaced by sodium phosphate. The speed of rotation used was 40 rpm.

The dissolution medium used in the Paddle Method was 900 ml distilled water and the speed of rotation 100 rpm. The potassium released into the medium was estimated by atomic absorption spectrophotometry as described earlier, except that no standard-addition method was used.

RESULTS

Bioavailability

Bioavailability was calculated by dividing the mmol K^+ excreted in 24 h by the dose of potassium administered (40 mmol). These results are shown for each subject in Table 4 under column B. The volume of urine voided in 24 h and the cumulative excretion of potassium are given for each subject for each day in Table 3. The difference in the amount of potassium excreted on days 4 and 3 and also the difference between amount excreted on day 4 and the mean of excretion on days 2 and 3 (Δ mmol K^+ per 24 h) are shown in Table 4.

Analysis of the amount of potassium excreted in the individual urine fractions showed that all subjects, though to a lesser extent subject G.St., excreted markedly higher amounts of potassium after oral ingestion of the two preparations under test. An increased excretion of potassium compared to that on control day 3 was generally observed for up to 7 h after administration. In the majority of subjects, this increase was apparent for up to 18 h.

As shown in Table 3, considerable inter-subject differences in mmol K^+ excreted occurred, which gave a coefficient variation (CV) of 14.9% with a mean total excretion of

TABLE 3

CUMULATIVE EXCRETION OF POTASSIUM (mmol) PER 24 h, WITH THE URINARY VOLUME SHOWN IN PARENTHESES

Subject	KCl retard Zyma				Kalitrans retard			
	Day 1	Day 2	Day 3	Day 4	Day 1	Day 2	Day 3	Day 4
S.L. A.	88.3 (1090)	102.3 (1600)	92.9 (1134)	148.1 (1145)	77.7 (1700)	87.4 (1250)	103.7 (1165)	145.0 (1141)
U. K.	78.8 (1070)	94.9 (1270)	94.1 (1121)	144.0 (907)	92.3 (940)	71.7 (730)	86.2 (791)	130.6 (1015)
M. L.	101.7 (1550)	100.6 (1500)	80.6 (773)	137.5 (1349)	105.7 (1260)	113.4 (1690)	97.8 (1173)	139.7 (1556)
K. M.	80.2 (900)	89.4 (1060)	90.2 (1096)	132.3 (1132)	95.1 (930)	75.3 (920)	81.6 (1015)	137.7 (1799)
G. R.	91.8 (1320)	75.6 (1540)	86.3 (1385)	106.2 (1235)	101.6 (1600)	84.7 (1035)	101.7 (1124)	131.3 (1337)
K. R.	79.4 (1940)	78.0 (1390)	105.7 (1485)	139.4 (1363)	114.2 (1860)	108.1 (1680)	102.7 (1269)	152 4 (1563)
R. Sch.	116.7 (1460)	120.6 (1600)	101.4 (942)	130.2 (846)	117.4 (1160)	124.8 (1065)	132.0 (939)	160.4 (965)
E. Schm.	70.4 (790)	86.4 (1320)	89.8 (956)	119.7 (1299)	91.9 (960)	102.5 (1150)	110.6 (1316)	133.7 (1200)
U. Schm.	99.4 (1580)	97.3 (1340)	124.4 (1437)	142.8 (1278)	99.9 (2220)	97.7 (810)	115.2 (1419)	131.1 (1330)
G. St.	86.7 (1115)	108.8 (1090)	74.3 (1530)	128.4 (1676)	55.2 (710)	50.7 (620)	57.8 (1166)	112.5 (1329)
x	89.3 (1281)	95.4 (1371)	94.0 (1185)	132.9 (1223)	95.1 (1334)	91.6 (1095)	98.9 (1137)	137.4 (1323)
CV (%)	15.2 (27.6)	14.4 (14.2)	14.9 (21.9)	9.5 (19.4)	19.0 (36.6)	24.1 (33.3)	20 5 (16.2)	9.6 (19.7)

x = mean value; CV = coefficient variation.

TABLE 4

DIFFERENCE BETWEEN AMOUNTS OF POTASSIUM EXCRETED PER 24 h ON CONTROL DAYS 3 OR 2 + 3 AND THAT EXCRETED AFTER ADMINISTRATION OF 40 mmol K (ΔK mmol/24 h). THE CALCULATED BIOVAILABILITY VALUES (B) ARE ALSO SHOWN (ΔK mmol PER 24 h/ADMINISTERED DOSE OF 40 mmol K).

Subject	KCl retard Zyma				Kalitrans retard			
	ΔK mmol/24 h (Day 4 vs Day 3)	B	ΔK mmol/24 h (Day 4 vs mean of days 2 + 3)	B	ΔK mmol/24 h (Day 4 vs Day 4)	B	ΔK mmol/24 h (Day 4 vs mean of days 2 + 3)	B
S.L. A.	55.2	1.38	50.5	1.26	41.3	1.03	49.4	1.24
U. K.	49.9	1.25	49.5	1.24	44.4	1.11	51.6	1.29
M. L.	56.9	1.42	46.9	1.17	41.9	1.05	34.1	0.85
K. M.	42.1	1.05	42.5	1.06	56.1	1.40	59.2	1.48
G. R.	19.9	0.50	25.2	0.63	29.6	0.74	38.1	0.95
K. R.	33.7	0.84	47.5	1.19	49.7	1.24	47.0	1.18
R. Sch.	28.8	0.72	19.2	0.42	28.4	0.71	32.0	0.80
E. Schn.	29.9	0.75	31.6	0.79	23.1	0.58	27.1	0.68
U. Schm.	18.4	0.46	31.9	0.80	15.9	0.40	24.6	0.62
G. St.	54.1	1.35	36.8	0.92	54.7	1.37	58.2	1.46
x	38.9	0.97	38.2	0.95	38.5	0.96	42.1	1.06
s	14.7	0.4	10.9	0.3	13.7	0.3	12.6	0.3
CV (%)	37.8	37.70	28.6	30.1	35.5	35.4	29.9	29.9

x = mean value; s = standard deviation; CV = coefficient variation.

94 mmol K^+ on control day 3 prior to administration of KCl retard Zyma, and a CV of 20.5% with a mean total excretion of 98.9 mmol K^+ prior to administration of Kalitrans retard. Following oral administration of 40 mmol K^+ via the two preparations, there was a marked increase in the mean cumulative excretion of K^+ to 132.9 mmol (CV 9.5%) after KCl retard Zyma and to 137.4 mmol (CV 9.6%) after Kalitrans retard. As shown in Table 4, the difference (Δ mmol K^+/24 h) in mean total potassium excreted by all subjects on day 3 and that on day 4 after KCl retard Zyma is 38.9 mmol K^+ (CV 37.8%), and that for Kalitrans retard is 38.5 mmol K^+ (CV 35.5%). These results are not significantly different if the difference is calculated on the basis of the mean of cumulative excretion on days 2 and 3 (KCl retard Zyma 38.2 mmol K^+ (CV 28.6%) Kalitrans retard 42.1 mmol K^+ (CV 29.9%)). Comparison of the bioavailability values (B) calculated from these two sets of figures also showed no significant difference between the two preparations – KCl retard Zyma 97% (CV 37.7%) and 95% (CV 30.1%), Kalitrans retard 96% (CV 35.4%) and 106% (CV 29.9%).

In the majority of subjects, analysis of the urine fractions after administration of the two preparations showed a clear increase of potassium excretion which lasted for at least 7 h. Examples of such results are shown graphically in Figs. 1–4, which depict results from subjects K.M. and K.R.

Although the bioavailability values for the two preparations calculated for these two subjects were not identical (Table 4), the results clearly show that a delayed, sustained renal excretion of potassium can be expected with the tablet preparation KCl retard Zyma and the pellet preparation Kalitrans retard, which leads to elevated levels of urinary potassium for up to 18 h.

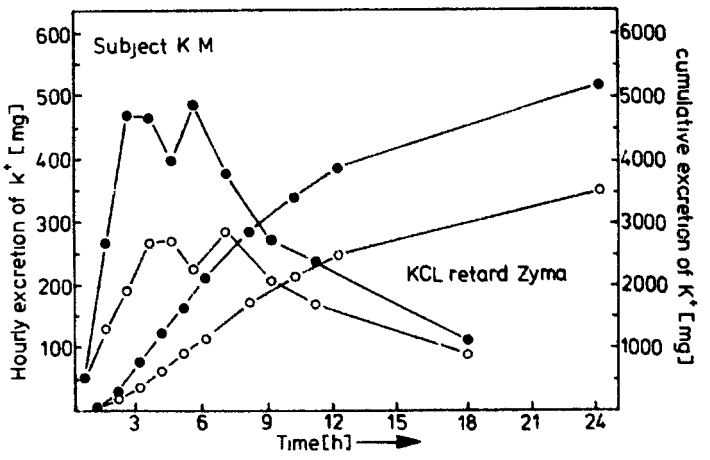
Pharmaceutical availability

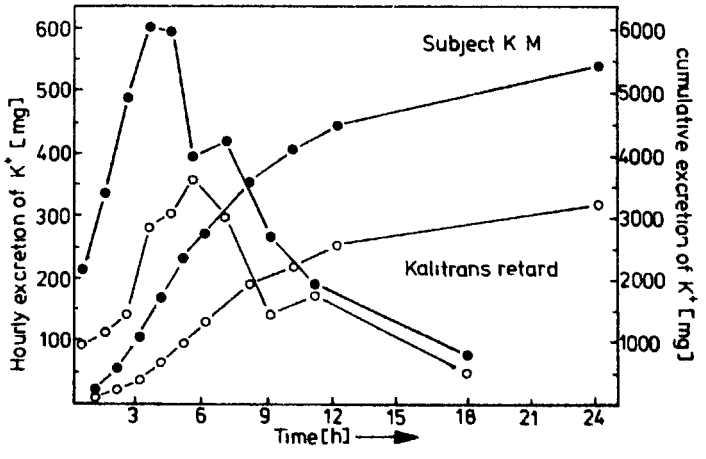
The two preparations gave quite different results when their dissolution rates were measured using the Rotation Method NF XIV, which has been proposed as an in vitro technique suitable for testing the pharmaceutical availability of sustained release preparations. Within the first hour, 73% of active ingredient had already been released from KCl retard Zyma, but only 30% from Kalitrans retard (Table 5). Whilst the release of potassium from the pellet preparation lasted throughout the experimental period of 7 h, all the

TABLE 5

PHARMACEUTICAL AVAILABILITY OF KCl RETARD ZYMA AND KALITRANS RETARD AS MEASURED BY THE ROTATION METHOD NF XIV (A) AND THE PADDLE METHOD USP XX (B)

	% of declared content of KCl released after various times (h)				
	1.0	2.0	3.5	5.0	7.0
KCl-retard Zyma (A)	73.0%	96.0%	102.0%	102.0%	102.0%
KCl-retard Zyma (B)	16.0%	35.0%	50.0%	73.0%	88.0%
Kalitrans retard (A)	29.7%	40.2%	49.0%	97.7%	99.9%
Kalitrans retard (B)	18.0%	38.0%	51.0%	75.0%	86.0%


Subject K M
KCL retard Zyma
Hourly excretion of K⁺ [mg]
cumulative excretion of K⁺ [mg]
Time [h]
600
500
400
300
200
100
6000
5000
4000
3000
2000
1000
3
6
9
12
15
18
21
24


Subject K M
Kalitrans retard
Hourly excretion of K⁺ [mg]
cumulative excretion of K⁺ [mg]
Time [h]
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500
400
300
200
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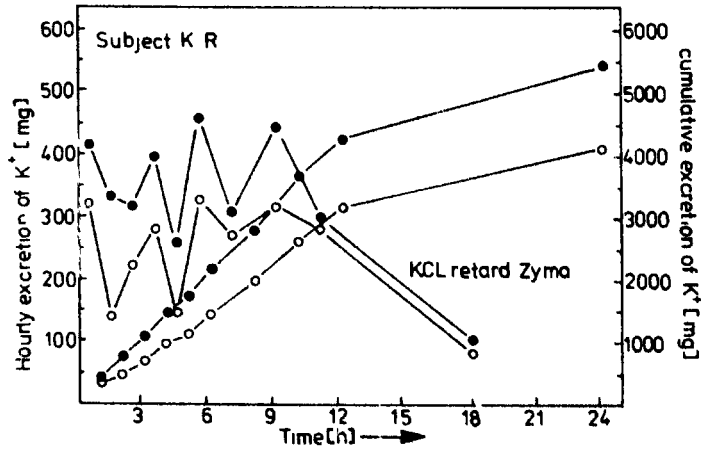
2000
1000
3
6
9
12
15
18
21
24


Subject K R
KCL retard Zyma
Hourly excretion of K⁺ [mg]
cumulative excretion of K⁺ [mg]
Time [h]
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500
400
300
200
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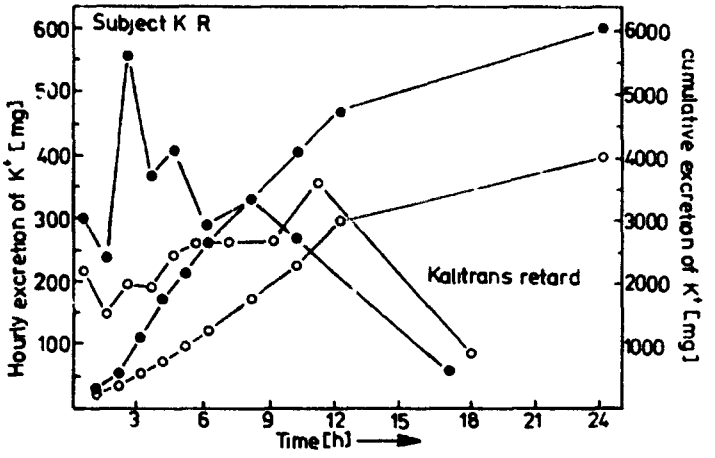
2000
1000
3
6
9
12
15
18
21
24



Figs. 1–4. Hourly and cumulative urinary excretion of potassium following oral administration of sustained release preparations of potassium chloride. o———o, potassium excretion on control day 3; •———•, potassium excretion after oral administration of 40 mmol K^+.

active ingredient had been released from the tablet preparation within 3.5 h. Contrasting results were obtained with the Paddle Method. Here the preparations showed very similar release profiles in which a total of 90% of active ingredient was slowly released over 7 h from both preparations.

DISCUSSION

During investigations into the bioavailability of potassium-containing preparations, problems were often found due to the non-standardization of dietary intake, because an uncontrolled ingestion of potassium immediately causes a change in the pattern of urinary potassium excretion. Carefully controlled diets should therefore be given in bioavailability studies to ensure a continual, constant supply of potassium. In our opinion, the diet used in these investigations was satisfactory since it provided a steady intake of potassium, particularly in the first 8 h after administration of the preparations when fluctuating levels of ingested potassium could interfere with the results. The increased urinary excretion of potassium observed after the two preparations can therefore be said to reflect the release characteristics of the two drugs.

Studies of the bioequivalence of sustained release preparations containing potassium generally require approximately 40 mmol K^+ to be given orally if clear differences in potassium excretion compared to control days are to be shown. Experiments, in which a single application of some 8 mmol K^+ was given, showed that because of the intra- and intersubject variations, no significant differences in potassium excretion could be demonstrated before and after administration. Oral doses of 40–50 mmol K^+ have also been used by other authors in investigations into biological availability (Ben-Ishay and Engelman, 1973; Tannen and Cordano, 1978).

During the control days, the subjects excreted a mean total of 89–99 mmol K^+ (Table 3). The degree of interindividual variation in potassium excretion was reflected in

the coefficients of variation lying between 14 and 24%. The bioequivalence of the two preparations, KCl retard Zyma (coated tablets) and Kalitrans retard (capsules containing pellets of KCl), was shown by their similar bioavailability values of 97% (CV 37.7%) and 96% (CV 35.4%) respectively. The urinary excretion profiles of the two preparations were also similar.

These results are in direct contrast with those of other authors who have reported bioavailability values of KCl depot tablets of only 27% (Ben-Ishay and Engelman, 1973) and 47% (Tannen and Cordano, 1978). Such low bioavailability values were, in our opinion, obtained because the renal excretion of potassium after a single administration was only measured for 8 h.

In our studies of pharmaceutical availability using the Rotation Method, the declared content of active ingredient had been completely released from the depot tablet KCl retard Zyma within 3.5 h, whereas total release from the pellet preparation Kalitrans retard took at least 7 h. These differences in in vitro dissolution rates of preparations, which have been shown to be bioequivalent, indicates that the chosen speed or rotation of 40 rpm was too high. Thus a much lower intensity of movement must be used if the in vitro results are to be comparable with those obtained in vivo. Such an adjustment in speed of rotation in the light of bioavailability data has already been mentioned in the NF XIV (National Formulary).

As already shown in other investigations, the high intensity of movement in the Rotation Method causes rapid disintegration of tablets where the active ingredient is embedded in a matrix (Steinbach and Möller, 1977 and 1979). Studies with the Paddle Method USP XX, in which a lower degree of mechanical stress is applied, show that the release of active ingredient was slower than with the Rotation Method NF XIV. Thus with the Paddle Method, the release was sustained over a period of 7 h and is comparable to that from the pellet preparation Kalitrans retard. Experiments in which the rate of dissolution was measured using the Disintegration Tester of the USP, have also shown a slow rate of release from KCl retard Zyma tablets (Gumma et al., 1971). Further confirmation of these results is given by the in vivo bioavailability studies reported here and in radiographic pictures taken over 1–4 h after oral administration of the tablets in man (Freytag, 1977).

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